## REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office action dated August 9, 2005 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

I. The Amendments

Claims 2-6, 8-9, 14, 17-19 are canceled without prejudice. Applicant reserves the right to pursue the subject matter of these claims in a continuing application.

Claim 1 is amended to recite a method for treating a skin wound comprising transforming amniotic epithelial cells with one or more recombinant expression vectors encoding a bioactive protein. Basis for these amendments can be found, for example, on page 19, lines 30-33 and page 20, lines 13-29. Claim 1 is further amended to recite culturing the transformed cells, as described for example on page 19, lines 30-31. Claim 1 is also amended to recite administering the transformed cells topically to the skin wound, the cells being supported on a membrane substrate. Basis is found, for example, on page 19, lines 6-7, lines 29-30, and lines 30-33.

Claim 7 as amended and new claim 21 recite the bioactive protein is a growth factor. Basis is found, for example, on page 20, lines 13-16.

Claims 10, 12, 13, 15, and 20 are amended for standard terminology.

Claim 16 is amended to recite a topical system for treating a skin wound comprising transformed amniotic epithelial cells and a membrane substrate. Basis is found, for example, on page 19, lines 30-33 and page 20, lines 13-29.

New claims 22 and 24 find basis in original claim 7.

New claim 23 finds basis in original claim 12.

No new matter is added by way of these amendments.

II. Claim Objections

Claim 8 was objected to for lacking a conjunction between "animal cells" and "mammalian cells." Claim 8 is canceled. Accordingly, Applicant respectfully request withdrawal of the objections to this claim.

III. 35 U.S.C. §112, first paragraph

Claims 1-10 and 12-20 were rejected under 35 U.S.C. §112, first paragraph, allegedly because the specification does not enable any person skilled in the art to which it pertains, or with which it is most connected, to make and use the invention commensurate in scope with the claims. Specifically, the Examiner found the specification to lack enablement for obtaining the desired effects other than wound healing, for delivering molecules other than growth factors, or for methods of delivering molecules to sites other than the site of cell administration.

It is Applicants believe that the amended claims address many, if not all, of the Examiner's concerns. The Examiner has admitted that methods of improving wound healing by administration of epithelial cells modified to express growth factors is considered to be enabled (page 6, Office action). Applicants have amended the claims accordingly, with the exception of a limitation that the transfected cells express a growth factor. Applicants submit that transfection of epithelial cells for expression of biomolecules other than growth factors is enabled, for the following reasons.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. M.P.E.P. § 2164.01. Applicants respectfully ask the Examiner to consider the following:

1. The present claims require transfection of amniotic epithelial cells with a vector encoding for a bioactive protein and expression of the protein after topical application of the cells to skin wound.

2. Example 8 in the specification provides a working example for preparation of a retroviral vector and transduction of amniotic epithelial cells to express marker proteins and platelet-derived growth factor-beta (PDGF-β) (see Application pages 36-38).
3. Guidance for selection of bioactive proteins is given on page 20, lines 13-29.
4. Preparation of recombinant expression vectors is routine in the art as evidenced by over 26,000 articles available on the PubMed database (www.ncbi.nlm.nih.gov/entrez) referencing the terms "vector," "expression," and "protein." Additionally, searches on the PubMed database for the terms "expression," "vector," and one of "PDGF," "FGF," "GM-CSF," "HGH," "defensin," or "TIMP" yielded 130, 126, 230, 47, 43, and 72 articles, respectively. Thus, it is well within the general knowledge in the art to prepare a recombinant expression vector encoding any of the bioactive proteins noted in Applicant's specification.
5. Transfection of expression vectors into cells in vitro is easily accomplished, as evidenced by Example 8.
6. Expression of the encoded protein upon topical application of the transformed cells to a skin wound is entirely expected and predictable, based on the in vitro studies described by Applicant and the prior art noted by the Examiner.

In light of the amendments to the claims, the teachings in the specification, and the skill and knowledge of one skilled in the art, it is believed that the claims as set forth an enabled. Withdrawal of the rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

IV. 35 U.S.C. §102

Claims 1-5, 7-10, 12, 13, 16-18, and 20 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Faulk et al. (*Lancet*, 1(8179):1156-1158, 1980) as evidenced by Uchida et al. (*J. Neurosci. Res.*, 62:585-590, 2000).

Claims 16-19 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Eming et al. (*Biotech. Bioeng.*, 52(1):15-23, 1996).

Applicant respectfully traverses these rejections.

A. The Present Claims

Amended claim 1 relates to a method for treating a skin wound comprising (i) transforming amniotic epithelial cells with one or more recombinant expression vectors encoding a bioactive protein, (ii) culturing the transformed cells, and (iii) administering the transformed cells topically to the skin wound, said cells being supported on a membrane substrate, whereby the cells contact the skin wound for expression of the bioactive protein for treating the skin wound.

Claim 16, as amended, embodies a topical system for treating a skin wound, comprising (i) amniotic epithelial cells transformed with one or more recombinant expression vectors encoding a bioactive protein for expression of the bioactive protein by the transformed cells; and (ii) a membrane substrate, such that said cells are supported on the membrane substrate so as to contact the skin when topically applied.

B. The Cited References

FAULK ET AL. describe unmodified amniotic membranes to promote wound healing.

EMING ET AL. relate to a genetically modified skin graft for the local synthesis and delivery of wound-healing growth factors. Epithelial cells were modified by retroviral-mediated gene transfer to include copies of the genes encoding platelet-derived growth factor or insulin-like growth factor-1.

C. Analysis

According to the M.P.E.P. § 2131, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."

1. Rejection over Faulk et al.

With regard to claim 1, Faulk et al. fail to teach transforming amniotic epithelial cells with one or more recombinant expression vectors encoding a bioactive protein. Nor do Faulk et al. teach a topical system comprising amniotic epithelial cells transformed with one or more recombinant expression vectors encoding a bioactive protein as in claim 16. Instead, Faulk et al. teach the use of unmodified amnion membranes.

2. Rejection over Eming et al.

Eming et al. fail to teach a method for treating a skin wound comprising transforming amniotic epithelial cells as in amended claim 1. Nor do Eming et al. teach a topical system including transformed amniotic epithelial cells as in present claim 16. Instead, Eming et al. teach transforming human diploid keratinocytes for production of a modified skin graft.

As Faulk et al. and Eming et al. fail to teach each and every element as presently claimed, Applicant submits that standard of strict identity to maintain a rejection under 35 U.S.C. § 102 has not been met. Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. § 102.

V. 35 U.S.C. §103

Claims 1-10 and 12-20 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Faulk et al. in view of Eming et al. and Sakuragawa (U.S. Patent No. 6,117,676).

Claims 1-10 and 12-20 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Faulk et al. in view of Eming et al., Sakuragawa and Pollock *et al.* (U.S. Patent No. 6,191,269).

Claims 1-10, 12, and 14-20 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Klein et al. (U.S. Application No. 2003/0091543) in view of Sakuragawa (*Cell Transplantation*, 4(3):343-346, 1995) taken with the evidence of Marshall (U.S. Patent No. 6,479,052).

Applicant respectfully traverses these rejections.

A. The Present Claims

The presently pending claims are summarized in IV above.

B. The Cited Art

FAULK ET AL. is described above.

EMING ET AL. is described above.

SAKURAGAWA relates to amniotic cells in which a gene desired to be expressed is introduced as cell suspension for injection.

POLLOCK ET AL. describe compositions and methods for selective induction of apoptosis in cancer cells.

KLEIN ET AL. describe a biological preparation including genetically modified cells together with biocompatible matrices.

MARSHALL ET AL. disclose a method of adhering cells to a target surface by coating the target surface with a mixture of a first component comprising a non-polymeric fibrin-related protein and a second component effective for converting the fibrin-related protein to fibrin polymer; and spraying a suspension of the cells onto the coated target surface, wherein the mixed two components have formed a fibrin polymer with a tack effective to adhere the cells.

C. Analysis

According to the M.P.E.P. § 2143, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (or references when combined) must teach or suggest all the claim limitations."

1. Rejection over Faulk et al. in view of Eming et al. and Sakuragawa

The references, taken alone or in combination, fail to show or suggest all of the claimed features. As noted above, the present claims relate to treating a skin wound by topically applying transformed amniotic epithelial cells to the wound, for expression of a bioactive protein for treating a skin wound.

The Examiner proposes it would be obvious to modify the method of Faulk et al. by transfecting the amniotic cells of Faulk et al. with the vector Eming et al. used to transfect skin keratinocytes, based on a motivation supplied by Sakuragawa that amniotic epithelial cells offer immunological benefits.

Faulk et al. are concerned with treating wounds, such as leg ulcers, by applying amnion to the ulcer. The amnion, consisting of the single-celled layer of amnion epithelium and its basement membrane, is placed on the ulcers to promote healing by virtue of its natural angiogenic factors. Modification of Faulk et al. to use transfected amnion epithelial cells would necessarily require harvesting the cells, transfecting the cells, culturing the transfected cells, selection of the transfected cells, etc., a process that destroys the natural angiogenic factors sought in the therapy described in Faulk et al.

Moreover, nothing in the teachings of Faulk et al., Eming et al, or Sakuragawa when combined provides an expectation of success for treating skin wounds with transfected cells topically applied on a support. Eming et al. shows

successful transformation of skin keratinocytes, cells that were well studied in 1996 (see page 15, right column of Eming et al.), but teaches nothing about amniotic epithelial cells. Sakuragawa shows transfection of amniotic epithelial cells in suspension form (Col. 6, line 23), but does not show that transfected amniotic epithelial cells can be grown on a substrate. There is nothing in the cited documents to support the allegation on which the rejection is based, that skin keratinocytes are essentially interchangeable for amniotic epithelial cells.

Thus, the combined teaching of Faulk et al., Eming et al., and Sakuragawa fail to show or suggest treating a skin wound with transformed amniotic epithelial cells or the topical system for treating a skin wound as presently claimed.

2. Rejection over Faulk et al. in view of Eming et al., Sakuragawa, and Pollock et al.

The deficiencies in the combination of Faulk et al., Eming et al. and Sakuragawa, are described above. The teaching in Pollock et al. does not cure the deficiencies of these references as this reference is merely cited for a teaching of different vectors and makes no mention of amniotic cells or of wound healing.

3. Rejection over Klein et al. in view of Sakuragawa taken with Marshall

The Examiner asserts it would be obvious to use the amniotic epithelial cells of Sakuragawa in the invention of Klein et al. because the transfection of amniotic cells as a group would result in transfection of amniotic epithelial cells and because Sakauragawa teaches the benefits of using amniotic epithelial cells.

Klein et al. teach a cell preparation graft comprising modified cells and a biocompatible matrix. Klein et al. describe amniotic cells among a list of 28 other types of cells, but fail to make any mention of using amniotic epithelial cells. There is nothing in the reference to direct one skilled in the art to choose an amniotic cell over the other cell types listed, let alone to select a cell type not listed. Applicants understand that the Examiner looks to Sakuragawa for selection of the cell type,

however the teaching ins Sakuragawa is limited to cells in suspension form and there is nothing to show or suggest that modified amniotic epithelial cells could be grown in such a way for administration on a support matrix.

The Marshall et al. reference is cited merely for a teaching that INTEGRA is a membrane and makes no mention of amniotic cells. Nothing in any of the references would lead one skilled in the art to pick the amniotic epithelial cell from Sakuragawa, which is administered by injection, and place it on a biocompatible matrix as in Klein et al.

In view of the above, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103.

VI. Conclusion

Applicant respectfully submits that the pending claims are in condition for immediate allowance. The undersigned invites the Examiner to call the undersigned at (650) 838-4410 with any questions or comments. The Commissioner is hereby authorized and requested to charge any deficiency in fees herein to Deposit Account No. 50-2207.

Respectfully submitted,
Perkins Coie LLP

Date: February 9, 2006

Jacqueline F. Mahoney
Registration No. 48,390

**Correspondence Address:**
Customer No. 22918